ANPRM: Summary of Comments

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The views expressed in this document are solely those of the author, and do not represent the official position of the U.S. Department of Health and Human Services or the Office for Human Research Protections.

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Question 24: The Common Rule has been criticized for inappropriately being applied to—and inhibiting research in-- certain activities, including quality improvement, public health activities, and program evaluation studies. Regarding quality improvement, for example, these activities are in many instances conducted by health care and other organizations under clear legal authority to change internal operating procedures to increase safety or otherwise improve performance, often without the consent of staff or clients, followed by monitoring or evaluation of the effects. It is far from clear that the Common Rule was intended to apply to such activities, nor that having it apply produces any meaningful benefits to the public. Indeed, its application to such activities, and requiring IRB review and compliance with informed consent requirements, might have a chilling effect on the ability to learn from, and conduct, important types of innovation. We seek comment on whether and, if so, how, the Common Rule should be changed to clarify whether or not oversight of quality improvement, program evaluation studies, or public health activities are covered. Are there specific types of these studies for which the existing rules (even after the changes proposed in this Notice) are inappropriate? If so, should this problem be addressed through modifications to the exemption (Excused) categories, or by changing the definition of "research" used in the Common Rule to exclude some of these studies, or a combination of both? And if the definition of research were to be changed, how should the activities to be excluded be defined (e.g.,	A strong majority supported clarifying the definition of research and/or broadening the exemptions. Commenters identified areas that can be removed from regulatory oversight: • Quality improvement • Public health • Program evaluation • History/oral history • Languages • Journalism • Healthcare operations • Other social sciences Note: Questions 24 and 25 were analyzed jointly.	Individual Comment: "I am writing to you to express my strong support for the current proposal to re-evaluate the rules governing human-subject research. As a professor of modern Chinese history, oral history is an important part of my research on Chinese responses to and cultural constructions of famines and floods…. Anyone who has conducted oral history, however, knows that the historian often learns of new interviewees as he/she conducts his/her work, and that the freedom to ask new questions based on information an interviewee has raised is absolutely crucial. This meant that the questions I actually asked interviewees in China often differed significantly from those the IRB had approved before I began my work… In sum, the demands of the IRB bear little resemblance to the actual process of conducting good oral history research, in China or elsewhere." (Comment #113) Oral History Association: "Negative experiences with Institutional Review Boards are now widespread, illustrating the arbitrariness, misunderstanding, and misapplication of the Common Rule. In more than a few cases, IRB rulings have

"quality improvement" or "program evaluation")? Are there some such activities that should not be excluded from being subject to the Common Rule because the protections provided by that rule are appropriate and no similar protections are provided by other regulations? With regard to quality improvement activities, might it be useful to adopt the distinction made by the HIPAA Privacy Rule (45 CFR 164.501(1)), which distinguishes between "health care operations" and "research" activities, defining "health care operations" to include "conducting quality assessment and improvement activities, including outcomes evaluation and development of clinical guidelines, provided that the obtaining of generalizable knowledge is not the primary purpose of any studies resulting from such activities"?		inhibited or prevented oral historians from carrying out legitimate research. Researchers, especially graduate students, have to apply for IRB clearance from their home institutions to listen to oral histories deposited by narrators themselves in public archives, with strict indications for their use. Even some IRBs that "exempt" oral history from research oversight under the "minimal risk" clause, tum around and require application if the research is to be published. The arbitrariness of boards across the country creates confusion and demonstrates poor understanding of what constitutes 'generalizable knowledge,' frequently leading to misapplication of rules." (Comment #1010)
Question 25: Are there certain fields of study whose usual methods of inquiry were not intended to or should not be covered by the Common Rule (such as classics, history, languages, literature, and journalism) because they do not create generalizable knowledge and may be more appropriately covered by ethical codes that differ from the ethical principles embodied in the Common Rule? If so, what are those fields, and how should those methods of inquiry be identified? Should the Common Rule be revised to explicitly state that those activities are not subject to its requirements?	See above.	American Association for Public Opinion Research: "AAPOR supports the proposal to revise the Common Rule to specifically exclude the common methods and practices of academic fields that do not typically seek, as their primary goal, to produce generalizable knowledge through interaction with human subjects (as currently defined in the Common Rule). These fields might include art, cultural anthropology, English, history, journalism, languages, literature, music, theater, and others." (Comment #575)

I. RISK-BASED PROTECTIONS: EXEMPT -- OVERALL

2. The recommendation that all such studies undergo administrative review would be eliminated. Researchers would file a brief "registration" form with their institution or IRB, and would be permitted to commence their research studies immediately after filing the form. Audits of a small percentage of studies would take place to ensure appropriate application of and compliance with the revised regulation.

Question 22c: Do researchers possess the objectivity and expertise to make an initial assessment of whether their research qualifies for the Excused category?	A strong majority opposed the notion that researchers possess the objectivity and expertise to make an assessment of exempt status.	University of Florida: "In our current practice of reviewing all "Exempt" and "Non-Human" study requests, UF finds that 70% of the protocols submitted do not meet all the requirements for their respective categories, because many researchers do not have the expertise or objectivity to make the initial assessment." (Comment #766)
Question 19: Regarding the Excused category, should there be a brief waiting period (e.g., one week) before a researcher may commence research after submitting the one-page registration form, to allow institutions to look at the forms and determine if some studies should not be Excused?	A majority favored establishing a brief waiting period. Note: Commenters interpreted this question in different ways. Some focused on the fact that the researcher could begin research within one week, while others focused on the opportunity for institutional review.	American Academy of Family Practice National Research Network: "As with Issue #15 and other changes this would be a great benefit to the researchers in meeting deadlines within grants. In conjunction with Issue #15 this would lighten the burden upon the IRB, the researcher and the respective staff. This would also act as an incentive for newer researchers who may be intimidated by the IRB process to contribute to the breadth of information." (Comment #214)
Question 21: Is it appropriate to require institutions holding a Federalwide Assurance to conduct retrospective audits of a percentage of the Excused studies to make sure they qualify for inclusion in this category? Should the regulations specify a necessary minimum percentage of studies to be audited in order to satisfy the regulatory requirements? Should some other method besides a random selection be used to	A strong majority were opposed to the auditing requirement. Note: Questions 21 and 22a-b were analyzed jointly.	University of Missouri: "Our institution currently employs a streamlined process to review Exempt studies … Any retrospective [auditing] process would decrease our current level of assurance and would require a new intrusive inquiry that will

determine which Excused studies would be audited?		be sure to anger researchers. Why not make the proposed "brief' application form complete enough so that the IRB staff will be able to make the proper call right away, before such research begins?" (Comment #584)
Questions 22a-b: Are retrospective audit mechanisms sufficient to provide adequate protections to subjects, as compared to having research undergo some type of review prior to a researcher receiving permission to begin a study? Might this new audit mechanism end up producing a greater burden than the current system?	See above.	AstraZeneca: "Allowing researchers to make their own determinations, without prospective independent review, will weaken protection for some subjects." (Comment #535)
Question 22f: And will the use of a one-page registration form give institutions sufficient information to enable them to appropriately conduct the audits?	A majority did not believe a one-page form would be sufficient to conduct an audit.	University of Kentucky: "A one-page registration would not be adequate to audit a study. It would be necessary to include the investigator's justification for why the procedures meet the category of "excused" on the registration form." (Comment #625)

I. RISK-BASED PROTECTIONS: EXEMPT CATEGORY #2

3. The ANPRM does not suggest a specific change, but seeks public comment on whether a broad subset of studies using common social and behavioral science methodologies can be identified that should be eligible for exemption 2.

Question 15: Beyond the expansions under consideration, are there other types of research studies that should qualify for the Excused category? Are there specific types of studies that are being considered for inclusion in these expansions, that should not be included because they should undergo prospective review for ethical or other reasons before a researcher is allowed to commence the research?	A strong majority supported the inclusion of other types of research to qualify as Exempt. The most common were: • History • Ethnography/observation • Linguistics • Internet/virtual reality/online research • QI/QA	Western IRB: "One category of research studies that could be included in the excused category is the filming of subjects as they perform routine tasks. WIRB reviewed a study that involved facial recognition technology, and the research design was for subjects to walk on a given route through a populated area. It was not public observation because the subjects had to follow precise directions as directed by the researchers. The only research that should not be considered inclusion in the excused category of b2 is that which involves obtaining information about illegal activities that could be used in prosecution, or involves the possibility of extreme psychological reaction, such as watching extremely violent acts." (Comment #772)
Question 17a: What specific social and behavioral research methodologies should fall within the Excused category [2]?	A majority supported the inclusion of additional methodologies. Examples of recommended methodologies were: • Ethnographic research, social networking, virtual reality, online research, on-line gaming research, deception, behavioral tasks and minimal risk experimentation • Surveys and interviews, regardless of data collection mode (e.g., interviewer	Individual Comment: "Include all research that is limited to interactions with no interventions, as educational tests, surveys, interview procedures represent almost the universe of research of interactions. This will also make it clear that surveys or interviews designed to manipulate the subjects is not exempt." (Comment #592)

	administered via telephone, face-to-face, or via the internet, or self-administered via paper and pencil or internet), focus groups • Data collected from computer tasks, puzzles, eye tracking devices, keyboard strokes, mouse clicks, research on decision making • Interviews, surveys, focus groups, ethnographic and participant observation research, and oral histories with competent adults • De-identified surveys and/or data collection where no re-identification links are maintained • Focus groups with non-risky topics A minority, however, did not believe research methodology was an adequate criterion to make an Exemption determination, pointing out the importance of taking into consideration the specific topic of the study, and whether vulnerable groups are being studied.	

4. Exempt category 2 would be broadened by eliminating criteria (i) and (ii) for studies that involve competent adults, i.e., such research would be exempt even if the information was recorded in an identifiable way and the disclosure could pose such risks to the subject.

Question 16: Should research involving surveys and related methodologies qualify for the Excused category only if they do not involve topics that are emotionally charged, such as sexual or physical abuse? If so, what entity should be responsible for determining whether a topic is or is not emotionally charged?	A majority opposed the idea of excluding "emotionally charged" research from Exempt category #2. Four reasons most frequently: 1. The difficulty of defining "emotionally charged" 2. The belief that so-called "emotionally charged" topics do not place subjects at material risk 3. A desire to allow IRBs, not regulations, to decide what constitutes emotionally-charged research 4. The "slippery slope" concern – removing "emotionally charged" studies from the exempt category could make it more difficult for other "sensitive" research to get approval – see comment.	Individual Comment: "I conducted a survey of the Sociology of Sexualities Section of the American Sociological Association and found that almost half of the respondents had experienced difficulty getting their projects approved by their local IRBs. IRBs consistently withheld approval because of how committee members applied vague terms such as "risk" and "vulnerability." I found that many IRBs consider any research on sexuality to be inherently risky and therefore they demand extraordinary and often prohibitive methodological changes or measures for acquiring consent and ensuring confidentiality. The Common Rule, which is based on biomedical and behavioral research, has had the effect of completely blocking or substantially modifying certain areas of social science, such as sexuality studies." (Comment #614)

I. RISK-BASED PROTECTIONS: EXEMPT CATEGORY #4

5. Reforms [regarding research using existing biospecimens (clinical or from prior research)] would require written consent for research use of biospecimens, even those that have been stripped of identifiers. Consent could be obtained using a standard, short form by which a person could provide open-ended consent for most research uses of a variety of biospecimens (such as all clinical specimens that might be collected at a particular hospital). This change would only apply to biospecimens collected after the effective date of the new rules.

[Note: Regarding biospecimens: the ANPRM asked whether prior consent would be necessary for ***all* biospecimens**, unless a waiver was received. Regarding **data**, in contrast, the ANPRM suggested different rules, depending on whether the data were originally collected for a research purpose and whether the data were identifiable.]

Question 47: Should there be a change to the current practice of allowing research on **biospecimens** that have been collected outside of a research study (i.e. "left-over" tissue following surgery) without consent, as long as the subject's identity is never disclosed to the investigator?	A strong majority was opposed to the ANPRM suggestion.	American Society for Investigative Pathology: "*ASIP supports continuing the current practice of allowing research on biospecimens collected outside of a research study.* Use of archived tissues has made important contributions to medical care. For example, among the most significant advances in colon cancer research in the past decade has been the elucidation of an alternative mechanism for the development of colorectal cancer. This discovery, the serrated polyp pathway, is responsible for 30,000 new cases of colon cancer each year. The initial elucidation of the serrated polyp pathway resulting in mutations causing oncogene activation was accomplished using archived tissues. *Loss of ability to use certain types of archived tissues without obtaining consent may be the death knell of live-saving translational research*." (Comment #743. Italics added.) Australian National Health and Medical Research Council: "Chapters 3.4, 3.5 and 3.6 of the National Statement (2007) are currently under review, and it is expected that changes being made to

		those chapters will accord with the proposed changes to research using existing biospecimens (issue 2) further aligning the U.S. and Australian approaches." (Comment #247)
Question 49: Is it desirable to implement the use of a standardized, general consent form to permit future research on **biospecimens** and **data**? Are there other options that should be considered, such as a public education campaign combined with a notification and opt-out process?	The majority was favorable. Note: The wording of the question was unclear. Some commenters responded to the ANPRM concept of **requiring** a standard, general consent allowing for future research. Other commenters, in contrast, responded to the notion of having a standardized form **made available for use as desired**.	Individual Comment: "Implementation of a tiered consent model that allows research subjects to choose from among various categories of use would better allow people to make decisions about research participation… the evidence is mounting that most people agree to contribute to biospecimen research, but they want to be asked, as a matter of simple respect." (Comment #257) American Association of Medical Colleges: "AAMC is committed to the principle of obtaining informed consent when it is meaningful … An individual who is asked to sign a blanket consent document without any information about what type of research might be done in the future and with no opportunity to ask questions about the research that may be conducted (for example, if such consent is obtained just prior to surgery or on admission to a hospital) cannot be said to have provided meaningful informed consent. This could be more accurately characterized as "notice cloaked in consent's clothing," providing individuals with a false sense of individual control when, in fact, there is none." (Comment #706)

Question 23a: Under what circumstances should it be permissible to waive consent for research involving the collection and study of existing **data** and **biospecimens** as described in Section 3(a)(3) above [Exempt category 4]?[1]	A very strong majority favored allowing waiver of consent for the collection and study of existing data and biospecimens. The 2 most commonly mentioned circumstances: 1. Data are de-identified 2. Existing 116(d) waiver criteria are met	Individual Comment: Waiver should be allowed "If all of the following conditions are satisfied: Specimens and data were obtained with informed consent in circumstances conducive to voluntariness; specimens and data are no longer identifiable and cannot be re-identified; specimens and data will not be used or otherwise made available for cross-linking studies that could lead to re-identification or to identifiability; and strong enforcement mechanisms are in place to guard against violations and provide for individual remedy." (Comment #336)
Question 52: Should the new consent rules be applied only prospectively, that is, should previously existing **biospecimens** and **data sets** be "grandfathered" under the prior regulatory requirements? If so, what are the operational issues with doing so?	The nearly unanimous view favored the grandfathering of existing specimens and datasets.	Research Foundation for Mental Hygiene: "Careful record-keeping is necessary and stated upfront on the registration form. In essence, it becomes important for researchers to take note of the effective dates of new regs so that it is clear which studies should comply with them and, conversely, which studies would remain "grandparented" under previous regs." (Comment #238)

[1] Question 48 was similar: "What, if any, are the circumstances in which it would be appropriate to waive the requirement to obtain consent for additional analysis of biospecimens [collected for clinical use or for purposes other than for the currently proposed research]?"

I. RISK-BASED PROTECTIONS: EXPEDITED REVIEW

6. The ANPRM does not outline a specific change, but through questions seeks to determine whether some approval criteria do not meaningfully increase protections for subjects (i.e., in the case of studies that otherwise would qualify for expedited review).

Question 10: Which, if any, of the current criteria for IRB approval under 45 CFR 46.111 should not apply to a study that qualifies for expedited review?	Opinion was nearly evenly divided. Among persons who advocated that some 111 criteria should not apply, the two most commonly listed criteria were: 1. #6: Data monitoring 2. #2: Risks to subjects are reasonable	Methodist Hospital Research Institute: "All approval criteria should apply regardless of the risk level." (Comment #983) Catholic Health Initiatives: "CHI recommends that the following criteria for IRB approval not apply due to redundancy found in 45 CFR 46.111:" Criteria 1,2,3, and 8 (Comment #946)

7. This list [of approvable Expedited review categories] would be updated now, and at regular intervals, using appropriate data about risks to the extent possible.

Question 9: How frequently should a mandatory review and update of the list of research activities that can qualify for expedited review take place? Should the list be revised once a year, every two years, or less frequently?	Recommended review periods ranged from annually to every 5 years, with a mean of 2.9 years.	Dana-Farber Cancer Institute: "We agree that there should be a regular review of the research categories eligible for expedited review at an interval of no less than every three years in order to ensure that the categories are appropriately in sync with changing technologies that increase the number of minimal risk procedures encountered in routine physical and psychological examinations." (Comment #401)

8. Continuing review would not be required of studies that are eligible for expedited review unless the reviewer, at the time of initial review, determines that continuing review is required, and documents why.

Is it acceptable to eliminate continuing review for studies that qualify under any of the Expedited categories?	A strong majority favored removal of continuing review requirements for Expedited research.	North American Association of Central Cancer Registries: "We support eliminating continuing review requirements for 1) research approved as "minimal risk" studies that qualify for expedited review." (Comment #689)

I. RISK-BASED PROTECTIONS: CONTINUING REVIEW

9. Continuing review would generally not be required after all subjects in the study have completed all study interventions, and the only remaining procedures are standard-of-care procedures that are used to obtain follow-up clinical information (e.g., standard annual CT scans to detect any spread of the patient's cancer), and the analysis of the research data.

Question 3: For research that poses greater than minimal risk, should annual continuing review be required if the remaining study activities only include those that could have been approved under expedited review, or would fall under the revised exempt (Excused) category described in section 3, below (e.g., a study in which a physical intervention occurred in the first year, all subjects have completed that intervention, and only annual written surveys are completed for the next five years)?	A strong majority favored the ANPRM idea of not requiring annual continuing review for studies if the remaining stages could be considered as Expedited or Exempt.	American Educational Research Association: "There is no need for annual review of research greater than minimal risk when the remaining stages of the research would be expedited or excused under the new ANPRM categories (e.g., when routine surveys are being completed or the research is in the data analysis phase). If continuing review is required by reviewers, they should provide justification. OHRP should also provide guidance to support IRBs transition to and implementation of the elimination of continuing review in these phases of the research." (Comment #970)

II. SINGLE IRB REVIEW FOR MULTI-SITE STUDIES

10. For all of the U.S. sites in a multi-site study, the changes envision a single IRB of record.

Questions 30-33: Suggestion to require central IRB review for domestic sites involved in multi-site research.	This issue attracted a large number of comments, and revealed nearly evenly divided perspectives: • Researchers and disease advocacy groups tended to favor the single IRB review requirement. • IRB and institutional representatives tended to be opposed to the possible requirement, although many indicated single IRB review should be encouraged.	In favor: Pharmaceutical Manufacturers Association: "PhRMA strongly supports this concept because it could improve the efficiency of clinical research. A single IRB of record could eliminate the burdensome multi-IRB review process, which generally results in added expenses, time delays, and numerous revisions to the informed consent document, without added value to human subject protections." (Comment #675) Opposed: University of California: "UC has been using an "IRB of record" option for multi-site research on its campuses for several years… Yet, our experience is that even for multi-site research within the UC system, reliance by multiple sites on a single IRB of record can involve complexities that are a rational, legitimate basis for opting out of the agreement to rely on another campus IRB's review. Such complexities (including adverse event reporting, continuing reviews, conflicts of interest, radiation safety committee reviews, etc.) need to be accommodated and argue against the proposed mandate to use a single IRB." (Comment #408)

Question 34: If there was only one IRB of record for multi-site studies, how should the IRB of record be selected? How could inappropriate forms of "IRB shopping"—intentionally selecting an IRB that is likely to approve the study without proper scrutiny—be prevented?	Recommended criteria for selection of the IRB of record: 1. Location of PI 2. Being accredited/meet objective criteria 3. Expertise in this area of research, e.g., oncology, children 4. IRB that is being monitored/audited by federal agency Responses to the second question re: IRB shopping question tended to parallel responses to the first question. Some respondents indicated IRB-shopping was not a matter of concern.	Memorial Sloan-Kettering Cancer Center: "We suggest that for protocols initiated and written by a PI at a health-care institution (as opposed to studies originating in industry or NIH), the PI's local IRB should be the central IRB…." (Comment #699)

III. IMPROVING INFORMED CONSENT

11. The regulations would be revised to provide greater specificity about how consent forms should be written and what information they should contain. The goal would be consent forms that are shorter, more readily understood, less confusing, that contain all of the key information, and that can serve as an excellent aid to help someone make a good decision about whether to participate in a study.

Question 35: What factors contribute to the excessive length and complexity of informed consent forms, and how might they be addressed?	1. Contributory factors: • Regulatory/legal requirements • Institutional requirements • HIPAA • Fear of legal liability 2. Groups contributing to consent form length: • Sponsors • IRBs • OHRP/FDA 3. Which consent elements are contributing to excess length: • #2: All research risks • #1: Detailed study procedures	Group Letter from Academics and Practitioners in the Field of Human Computer Interaction: "We suggest that at least two factors contribute to the complexity and length of informed consent forms. First, institutional caution leads them to insert language that attempts to protect against even very low probability, low risk issues. Second, it's easier to get approval for a protocol from an IRB if it looks like one they previously approved, so investigators have an incentive to make as few changes as possible once they have an approved form." (Comment #719)
Question 40: Would informed consent be improved if the regulations included additional requirements regarding the consent process, and if so, what should be required? For example, should investigators be required to disclose in consent forms certain information about the financial relationships they have with study sponsors?	A very strong majority supported the requirement of investigator disclosure of financial relationships.	Kaiser Permanente: "Relevant financial or other interests of key study personnel should be disclosed to the participant." (Comment #711) Canadian Association of Research Ethics Boards: "Also important to note is the requirements for consent when conducting research with Aboriginal peoples. In Canada, community consultation and consent is required, in addition to individual consent." (Comment #533)

Question 37: Would the contemplated modifications improve the quality of consent forms? If not, what changes would do so?	A strong majority was in favor of the ANPRM concept. Most of the persons who *opposed* the ANPRM idea still favored the general concept, but were opposed to regulatory approaches that were viewed as overly-rigid.	Clemson University: "Finding ways to better achieve informed consent is very important to all those involved in human research protections. However, the idea of standardized consent forms feels too simplistic and rigid. The crux of human research protections lies in the subject's ability to understand the study and make an educated, informed decision about participation. Reducing that process to a standardized template is not likely to produce the intended result. Better guidance about language and methods would be welcomed and appreciated." (Comment #749)
Question 38: Should the regulations require that, for certain types of studies, investigators assess how well potential research subjects comprehend the information provided to them before they are allowed to sign the consent form?	A strong majority supported the development of regulations or guidance designed to encourage assessment of subject comprehension. In contrast, some of those opposed argued the regulations already have an implicit requirement to assure comprehension ("legally effective informed consent" and "in language understandable to the subject").	National Marrow Donor Program: "Although we do think that it is a good idea to assess how well potential subjects comprehend the information provided to them, we do not think that additional regulations will help to improve the situation. This issue should be addressed by other non-regulated means." (Comment #977)

IV. DATA PROTECTIONS TO MINIMIZE INFORMATION RISKS

12. Specified data security protections would apply to such research, calibrated to the level of identifiability of the information being collected.

Question 54: Will use of the HIPAA Privacy Rule's standards for identifiable and de-identified information, and limited data sets, facilitate the implementation of the data security and information protection provisions being considered? Are the HIPAA standards, which were designed for dealing with health information, appropriate for use in all types of research studies, including social and behavioral research? If the HIPAA standards are not appropriate for all studies, what standards would be more appropriate?	A strong majority was opposed to the use of the HIPAA standards for purposes of defining the identifiability of research data. Nearly all persons who answered the question about appropriateness of HIPAA standards for social and behavioral research expressed opposition to use of the HIPAA standards. Several commented the issue for social behavioral research is not the identifiability of data *per se*, but rather the level of risk inherent in the identifiability of data. Persons who were in support of the HIPAA standards tended to be persons based in medical organizations that were already following the HIPAA requirements.	American Association for the Advancement of Science: "AAAS recommends that HHS carefully weigh the burden it would impose by applying such a uniform security standard across disparate research fields. With regard to social and behavioral sciences, alternative or complementary approaches to HIPAA may be found in the current body of literature and corresponding federal agency policies that address data security with the goal of minimizing information risks." (Comment #920) Institute of Medical Biometry and Statistics, University of Lübeck, Germany: "In addition, the definition of "identifiable" used by the ANPRM does not distinguish between identification of an individual versus identification of a people-group (such as an isolated, genetically homogenous ethnic group). In such cases, we agree that the requirements should be set by the country (or setting, as in the case of Native Americans) where the genetic data were collected. (Comment #264)

Question 59: Would study subjects be sufficiently protected from informational risks if investigators are required to adhere to a strict set of data security and information protection standards modeled on the HIPAA Rules? Are such standards appropriate not just for studies involving health information, but for all types of studies, including social and behavioral research? Or might a better system employ different standards for different types of research? (We note that the HIPAA Rules would allow subjects to authorize researchers to disclose the subjects' identities, in circumstances where investigators wish to publicly recognize their subjects in published reports, and the subjects appreciate that recognition.)	A strong majority was opposed to the use of data security and information protection standards modeled on the HIPAA rules.	Public Responsibility in Medicine and Research: "Contrary to the suggestions made in the ANPRM, however, PRIM&R believes that HIPAA provides a poor model for protecting research privacy. It is a particularly poor model as applied to research data because much of HIPAA is concerned with authorizing the release of medical information to insurers, law enforcement, other providers, and so on." (Comment #834)

13. These [categories of] Exempt studies would no longer be fully exempt from the regulations. In particular, they would be subject to the new data security protections described above.

Question 61: Are there additional data security and information protection standards that should be considered [for Exempt research]? Should such mandatory standards be modeled on those used by the Federal government (for instance, the National Institute of Standards and Technology recently issued a "Guide to Protecting the Confidentiality of Personally Identifiable Information.")?	A strong majority opposed additional data security standards. A smaller number suggested a range of alternative approaches – see second comment.	Sage Bionetworks: "Continued IT innovation will make it hard for the Federal Government to maintain a standard that addresses new security technology opportunities and evolving risks from inappropriate access or use unless the guidelines are frequently updated and IRBs are equipped to implement them." (Comment #1053) Intermountain Health Care: "Intermountain believes that NIST standards may be well beyond the capability and resources of the common researcher. We recommend the following (once again, scalable to the size of the entity): 1. Assign accountability for security and privacy; 2. Train personnel on security and privacy standards; 3. Encrypt all back-up media, laptops, mobile

		devices, jump/USB and similar portable drives, and other devices that interact with and/or store identifiable research data; 4. Require access controls to prevent that data from being obtained, viewed, altered, or otherwise accessed by unauthorized users, and to prevent its systems from being compromised or breached; access audit logs 5. Not use or permit generic account logins; 6. Have adequate physical security controls in place at its data center and in all other areas or locations (physical or virtual) where data are stored or processed; 7. Adopt privacy and security policies and use them; 8. Perform periodic risk assessments and compliance audits based on privacy and security risks; 9. Encrypt data transmissions of identifiable data 10. Permit off-site storage or backups of data only in secure storage facilities; 11. Ensure that each entity's representatives (i.e., agents, contractors, and subcontractors) having access to the entity's data are bound by contractual obligations at least as stringent as the researcher's obligations; and 12. Require breach reporting similar to the current HIPAA standards to subjects (if necessary), to the institution providing the data, and to the IRB of record." (Comment #879)

V. DATA COLLECTION TO ENHANCE SYSTEM OVERSIGHT

14. A single web site would be created for the electronic reporting of all such events: this would meet all federal reporting requirements and the collected data would be stored in a single database. Reporting requirements would be harmonized across agencies.

Question 69: There are a variety of possible ways to support an empiric approach to optimizing human subject protections. Toward that end, is it desirable to have all data on adverse events and unanticipated problems collected in a central database accessible by all pertinent Federal agencies?	A strong majority indicated agreement in principle. However, many expressed practical concerns: • How such a system would operate • How the costs would be borne • How existing definitional differences would be resolved • Whether it would be more practical to only report *serious* AEs • How the data would be analyzed • Who would have access to the results • Whether this would duplicate existing AE reporting to sponsors and the FDA	Individual Comment: "Existing mechanisms pool reports and data on adverse events and unanticipated problems primarily with sponsors. This is often implemented with great variability and some confusion… a centralized database for reporting events should be established for each study that is multisite in nature, or involves devices or agents which may be utilized in single site studies. While DSMBs and sponsors would access for more detailed analysis, local IRBs, principal investigators and the public should have access to the data on file. The benefits to those designing studies yet to be approved could be significant. This should not replace any reporting requirements for DSMBs or sponsors. Uniformity in definitions and reporting would have a significant impact on present workloads for many principal investigators, struggling in a diverse and complicated arena of reporting." (Comment #742)

VI. EXTENSION OF FEDERAL REGULATIONS

15. Regulations would apply to all studies, regardless of funding source, that are conducted by a U.S. institution that receives some federal funding for human subjects research from a Common Rule agency.

Question 71: Should the applicability of the Common Rule be extended to all research that is *not* Federally funded that is being conducted at a domestic institution that receives some Federal funding for research with human subjects from a Common Rule agency?	Views were nearly evenly divided: • Some commenters who were in favor of the idea also wanted the Common Rule to apply to *all* research, even when not conducted in a university receiving federal research funding. • A number of commenters against the ANPRM suggestion expressed their opposition with emphatic language.	In favor: American Medical Informatics Association: "Most institutions that hold an OHRP-approved Federal-wide Assurance (FWA) already extend the applicability of the Common Rule to all research conducted in the institution… AMIA supports this proposal." (Comment #717) Opposed: Individual Comment: "No, I beg you, no. Most institutions apply 45CFR46 to all studies but having a small degree of flexibility here is important. OHRP is going to need to clarify reporting of non-compliance or hire a million people to deal with non-compliance from Expedited and now, as a result of these changes, Exempt studies." (Comment #17)

VII. HARMONIZATION OF REGULATIONS AND AGENCY GUIDANCE

16. The ANPRM does not present a specific change but through questions, seeks to determine whether or not the differences in guidance from agency to agency are justified by differences in the applicable statutes or missions of those agencies, and if not, to determine how to make guidance more uniform.

Question 74: If all Common Rule agencies issued one set of guidance, would research be facilitated both domestically and internationally? Would a single set of guidance be able to adequately address human subject protections in diverse populations and contexts, and across the broad range of research contexts (including biomedical, national security, education and other types of social and behavioral research)?	A very strong majority favored efforts to promote harmonized guidance. Even though the question was specific to agency *guidance*, commenters often remarked on *regulatory* differences among the Common Rule, FDA, and HIPAA.	UK National Health Service Research Ethics Committee NNT1: "The makers of the proposed rule might wish to consider the wider strategic objective behind these reforms. Their stated aim is to rationalise the legislative basis for medical research in the United States. But should their aims be wider than those currently stated? All NIH funded research bodies operating in Europe will be affected by the proposed changes. These bodies will nevertheless be subject to the national laws and research governance systems of the countries in which their research is to take place. It therefore makes sense at the outset to consider whether the prime objective of this rule change should be to harmonise US regulation to that applying in similar fields in other European member states. Consider the degree to which cross-border research could be stimulated if there was compatibility of governance requirements between the US and the European Union." (Comment #261) Individual Commenter who provided listing of inconsistencies: • Written procedures (HHS, FDA VA, DOJ, EPA) • Education (VA, DOD/DON) • Scientific review (VA, DOD, DOJ) • Resources (VA) • International research (HHS, FDA, VA, DOD) • Human Research Protections Program evaluation

		(VA, DOE) • Reporting of serious or continuing non-compliance (HHS, FDA VA, DOD) • Use of investigational test articles (FDA, VA) • Emergency use (HHS, FDA, VA) • IRB composition (HHS, FDA, VA) • Threshold for financial interest reporting/COI (HHS, FDA, VA) • Inclusion of children with disabilities (HHS, ED) • Criteria for exemptions (HHS, FDA, VA) • Convened meetings (HHS, FDA, VA) • Review using the expedited procedure (HHS, VA, DOD) • Report of unanticipated problems/AEs (HHS, FDA VA, DOD, DOE, DOJ) • Multi-site research (VA, DOD) • Plans for data and safety monitoring (HHS, FDA VA, DOD) • Review of advertising (FDA, VA, DOD, DOJ) • Protection of personally identifiable information (HHS, OCR, FDA, VA, DOJ, DOE) • Research-related injury (HHS, DOD, DOJ, VA) • Waiving or altering the consent process (HHS, FDA, VA, DOD, DOE) • Planned emergency research (FDA, VA, DOD) • Required records (HHS, VA) • Investigator qualifications (DOJ, VA, DOE) • Recruiting Study Subjects, Payment (HHS, FDA, VA, DOD) • Consent (HHS, FDA, VA, DOD, ED) (Comment #1027)